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ORIGINAL ARTICLE

SPLIT-COURSE RADIOTHERAPY IN STAGE IV HEAD & NECK CANCER

B.M.Biswal, Nik Ruzman, Nik Min Ahmad and Ahmad Zakaria

**Department of Nuclear Medicine, Radiotherapy & Oncology,
School of Medical Sciences, Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan, Malaysia**

Short course hypo-fractionated radiotherapy is a standard regime for the palliation of stage IV head and neck cancers. However few patients respond favorably and require further radiotherapy in curative intent. We have used split-course radiotherapy technique to find out this conversion rate from palliative to curative intent. This was a prospective study conducted from November 1998 to October 1999; twenty-six (26) patients with stage IV head & neck cancers were treated with a hypofractionated regime of radiotherapy. A tumor dose of 30 Gy in 10 fractions [time dose fraction (TDF) 62] over 2 weeks was delivered using a 6 MV linear accelerator. A conventional 2 field or 3 field technique was used. Patients were assessed for the regression of tumor on fifth day, tenth day of radiotherapy and 4 weeks after the completion of radiotherapy. Patients showing complete response and good partial response were allowed to receive further radiotherapy of 30 Gy in 15 fractions [TDF 49]. There were 21 males and 5 females in the study with a median age of 44 years (range 19-77 years). All patients completed the initial regime. Complete responses were observed among 14 patients (54%); partial response in 6 patients (23%), and no response was seen among 6 patients (23%). Sixteen patients (61%) were suitable for radical radiotherapy after phase-I course of the above schedule. Seventeen patients (65%) showed an improvement in the general well being with a better quality of life. One year actuarial survival was (76%), with a median survival time of 12 months. Split-course technique is a useful radiotherapy treatment in stage IV head and neck cancers to distinguish between the subset of patients who would require curative treatment and who would not.

Key words : *Split-course radiotherapy, head and neck cancers.*

Introduction

Head and neck cancers account for 5% of all malignancies world over, but the incidence is very high in some part of Asia which may be as high as 20% (1). The management options of cancers in these sites are surgery, radiotherapy or combination of surgery and radiotherapy. The 5-year cure rates by surgery or radiotherapy alone in their early stages (stage I & II) range from 70% to 90%. In late stages (stage-IV), the 5-year cure rate drops significantly to less than 10% (2). The poor results of head and neck cancers at the late stages are basically due to the large tumor volume, high intra-tumoral hypoxic cell fraction, and associated co-morbid medical illness, which complicate tissue tolerance. In general, palliative radiotherapy is recommended to treat majority of stage IV head and neck cancers. The aim of palliative radiotherapy is to relieve symptoms due to large tumor, infiltration to other structures, and control of discharge and bleeding. The palliative radiotherapy induced local control should be maintained for at least a reasonable period of time.

The standard radiotherapy dose schedule for palliation is 30 Gy in 10 fractions over a 2-week period. The above dose of radiation is supposed to

Table-1: Characteristics of study patients

Number of patients	***26***
Male : Female	***21:5***
Age	***44 years (19-77 years)***
Sites of primary (numbers)	***nasopharynx (11)***
	metastatic nodes (4)
	laryngopharynx (5)
	maxilla (2)
	tongue(2)
	palatine tonsil(1)
	cheek(1)
RT dose	***Phase-I 30Gy/10#/2 wks***
	Phase-II 30 Gy/15#/3 weeks
Response rate	***CR 54%***
	PR 23%
	NR 23%
Tumor regression rate	***mean 4 weeks***
Actuarial 12-month survival	***76%***

give durable tumor control at the local site. The response to radiation in squamous cell cancers of the head and neck varies due to many tumor related factors. Split-course radiotherapy is basically used in advanced cancers to differentiate between well-responding tumors from poorly responding tumors in various regimes and intervals. Previous studies in the past had tried split-course radiotherapy in lung cancer patients to differentiate between well-responding tumors from poorly responding tumors (3-4). Subsequently split-course technique has been used in head and neck cancer patients as an alternative to conventional fractionation (5-6). This technique of radiotherapy was found to be useful in bladder cancer, lung cancer and glioma of the brain (7-9). There are various fractionation schemes utilized for split-course radiotherapy including multiple doses a day schemes (10). Despite criticism for the use of split-course technique, current evidence shows that split-course technique is radiobiologically sound and produce similar results as conventional radiotherapy with less number of fractions and increased patient compliance (6,11). Here we would like to present our results of split-course radiotherapy in head and neck cancers.

Materials and Methods

The study was carried out between November 1998 to October 1999 in the division of Radiotherapy and Oncology of Hospital Universiti Sains Malaysia. Patients were subjected to selection criteria. Inclusion criteria were: patients with squamous cell carcinoma, age between 15 to 75 years, and Eastern Cooperative Oncology Group (ECOG) performance status between 1-3 were entered into the study. Patients with co-morbid illness like diabetes mellitus, connective vascular diseases, prior radiotherapy and chemotherapy were excluded from this study. A detailed demographic profile was recorded in a special form. The primary tumor was evaluated by either clinical estimation of the largest tumor extent in three dimensions or by the help of endoscope procedures. The neck nodes were measured in three dimensions before starting radiotherapy.

Classical two-field or three-field techniques was used to plan patients for radiotherapy. Radiotherapy was delivered in two phases. The phase-I consisted of 30 Gy in 10 fractions over 2 weeks (Time Dose Fraction [TDF] 62) and phase-II consisted of 30 Gy in 15 fractions over 3 weeks (Time Dose Fraction [TDF] 49). The dose was calculated at mid-plane for parallel-opposed fields and at 3-cms depth for direct anterior port to the lower neck. Wherever possible thermoplastic immobilization cast was used for accurate dose delivery and day-to-day reproducibility. In multifield techniques, treatment-planning computer was used to obtain optimal dose homogeneity. Measurable tumor volume was recorded in three dimensions on day-5 and day-10 of the phase-I radiotherapy course. After the completion of phase-I radiotherapy, the tumor volume (response) was again recorded at the

4th week. Patients achieving good response (complete response and some partial response with favorable performance status) were advised further radiation in phase-II. The response was classified as complete response (CR) if the regression was complete, partial response (PR) if the response was between 50-90%, and no response (NR) if the response was sub-optimal. The treatment related parameters and response to radiotherapy were analyzed and survival estimated using Kaplan-Meier survival analysis.

Results

Twenty-six head and neck cancer cases were eligible for this technique of radiotherapy. There were 21 men and 5 women with a median age of 44-years (range 19-77 years). All patients received the phase-I schedule of radiotherapy. Following phase-I radiotherapy, 16 (61%) patients achieved favorable response (all CR plus good PR cases) and recommended for further radiotherapy (phase-II) up to a radical dose (Fig 1a & Ib). There was a gradual trend of regression of tumor with a median regression period of 4-weeks (Fig-2). Complete response [CR] was observed among 14 (54%) patients, partial response [PR] in 6 (23%) patients, and no response [NR] in 6 (23%) patients (Fig-3). Seventeen (65%) patients showed improvement in the general well being with better Eastern Cooperative Oncology Group (ECOG) performance status. The follow-up period ranged between 4 to 20 months with a median survival time of 12 months (95% CI 8.22). Patients achieving CR showed better local control duration than PR or NR (Fig-3). Initial bulky tumor volume predicted a poor outcome. The 12-month actuarial survival rate was 76 % (Fig-4).

Discussion

In our study we observed a favorable outcome in split-course radiotherapy technique. From the 26 patients who were subjected to phase-I radiotherapy, 61% patients showed good response and subsequently received further radiotherapy up to radical dose. The response rate of tumors was 54% CR, 23% PR and 23% NR. Patients with no response developed disease progression or death by other intercurrent illness. The survival of stage IV head and neck cancers following full course of

Fig.1a: A case of advanced head and neck cancer with ulcerated right cervical lymph node

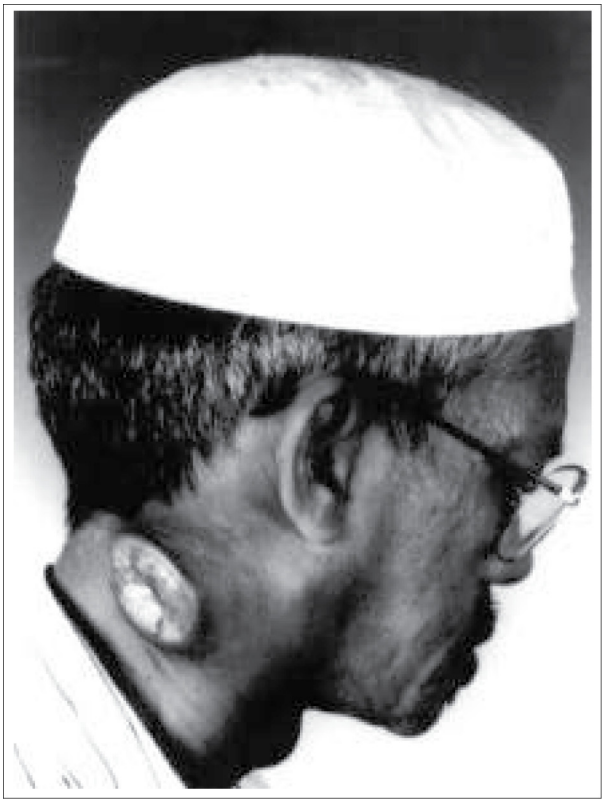
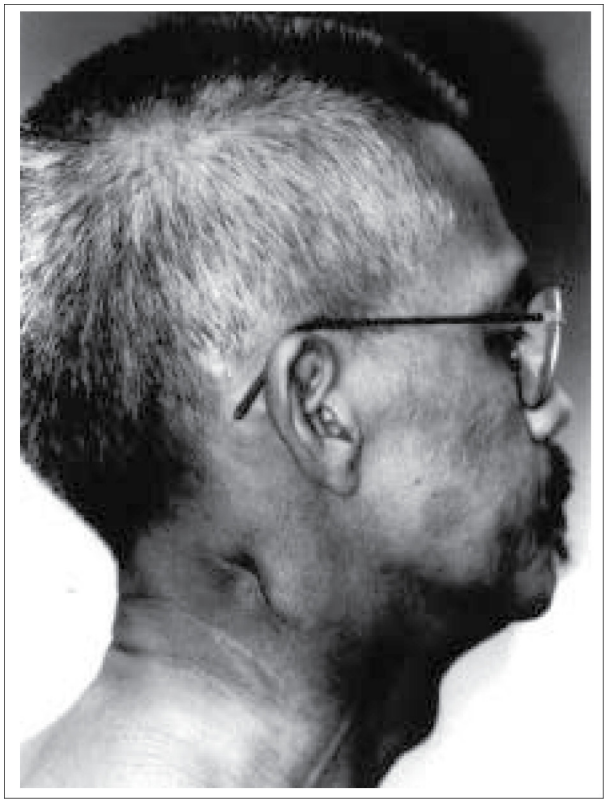


Fig.1b: Eight months following split-course radiotherapy patient achieved good local control of disease with healing of the ulcer

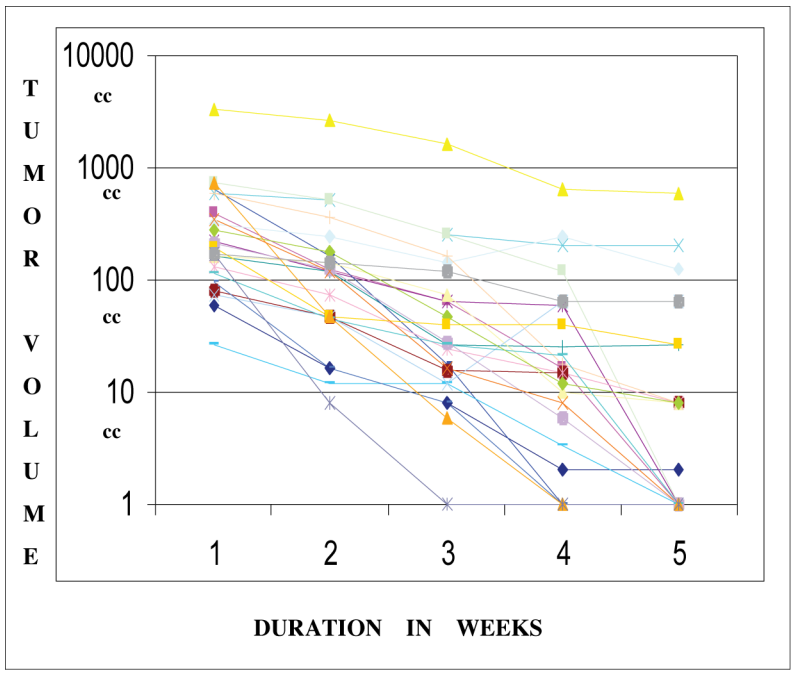


radiotherapy vary considerably from site to site and range from 10% to 30% at 5-years(2). The maximum number of treatment failures were encountered within first two years of follow-up. Better 5-year results were achieved with combined modality methods (12).

Fletcher et al introduced the principle of split-course radiotherapy for the treatment of advanced lung cancers (13). High-risk patients with non-small cell lung cancers (NSCLC) were recommended short-course of hypofractionated radiotherapy (30 Gy in 10 fractions over 2 weeks) and radiation response were reassessed after 4-8 weeks. Patients showing favorable response were subjected to further radiotherapy (30 Gy in 10 fractions) (8,13). This principle has been used in other tumor sites such as carcinoma of esophagus, anal canal cancer and brain gliomas (9,14-15). The conversion rate that proceeds from palliative to radical intent was up to 50%. In our study we found a conversion to radical intent was 61%, which allowed us to deliver radical dose of radiation.

In head and neck cancers, split-course radiotherapy is delivered in conventional fraction size (i.e. 180-200 cGy/fraction/day) with a mid-course split, or a rest period of 2-3 weeks. To reduce acute reactions, the overall treatment time of split-course radiotherapy is lengthened. Another split-course approach includes rapid fractionation of 3 Gy/fraction/day for 10 days with a 2 week split, followed by 3 Gy/fraction/day for another 10 days. The overall treatment course is approximately the same as conventional fractionated radiation therapy. Clinical experience indicates a lower control from split-course approach compared with continuous conventional fractionation radiotherapy (3-4). The inferior results are probably due to excessive repopulation and regeneration of the tumors, as the treatment interval was considerably prolonged. Rapid split-course radiotherapy may produce comparable local control rate as conventional fractionation, but at the cost of severe complications (16). The initial split-course trials were conducted with conventional fractionation and the inter-radiotherapy interval was about 4 weeks, which probably could give rise to increase in the number of resistant clonogens. Regarding treatment with high dose per fraction, it is very clear from the Christie Hospital, Manchester experience that radiation in higher dose per fraction delivered in conservative field techniques can result in good local control rate with minimal complications. Other studies by Barton et al showed the overall interval more than 4-6 weeks were compatible with tumor resistance (17). In split-course technique, the radiation was delivered immediately after establishing complete or good partial response within 4-weeks. Hence if we consider appropriate interval, field plan for radiation, and dose per fraction properly, then split-course radiotherapy technique could prove most effective in advanced head and neck cancers.

Fig.2: Graph showing pattern of tumor regression following radiotherapy



The principles of split-course radiotherapy in head and neck cancers have been blamed for the development of resistant clonogens due to increase in the hypoxic cell component. A recent study by Jund et al (11) showed a tendency of decrease in the hypoxic cell fraction after the respite. The main factor for resistance is the interval between two phases of radiotherapy course (17-18). Recently split-course radiotherapy is being used along with chemotherapy and altered fractionations (19).

The main aim of split-course radiotherapy in stage IV epidermoid cancers of the head and neck is to achieve good palliation, which was noticed among 65% of our patients. Secondly the conversion of intent of radiotherapy from palliative to radical intent was up to 61%. With this experience we suggest that split-course radiotherapy is a simple therapeutic test which should be tried in advanced head and neck cancers selected for radiotherapy. However in future, a combination of concurrent chemotherapy and altered fractionation might improve the outcome of this poor prognostic group of patients.

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Correspondence :

B. M. Biswal
Radiotherapy & Oncology
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan, Malaysia
Tel : +609-764 5417
Fax : +609-7653370
email : biswa@kb.usm.my

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Fig.3: Relation between response and survival in months

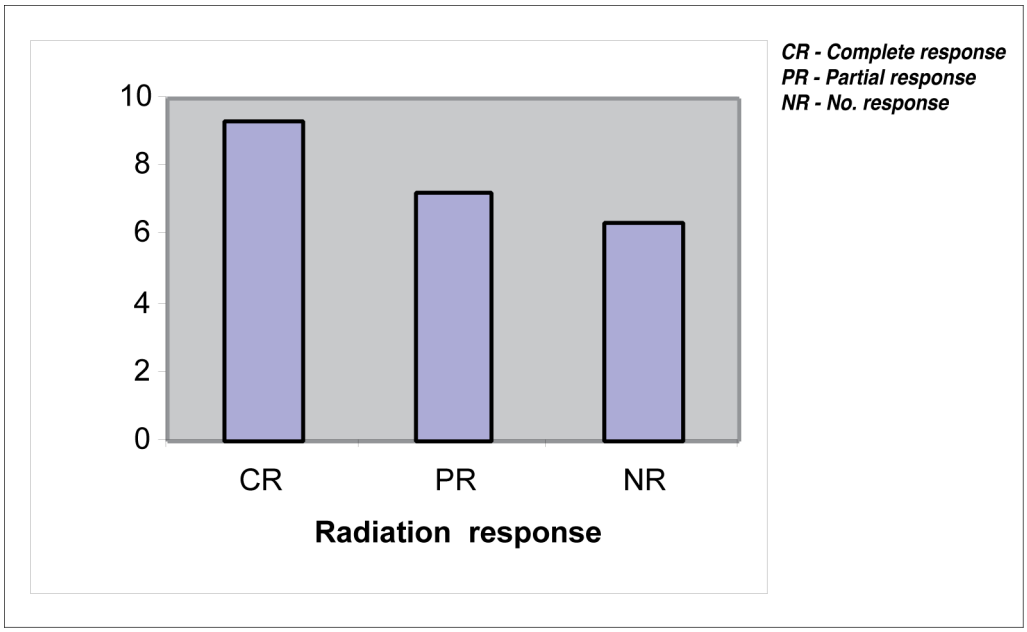
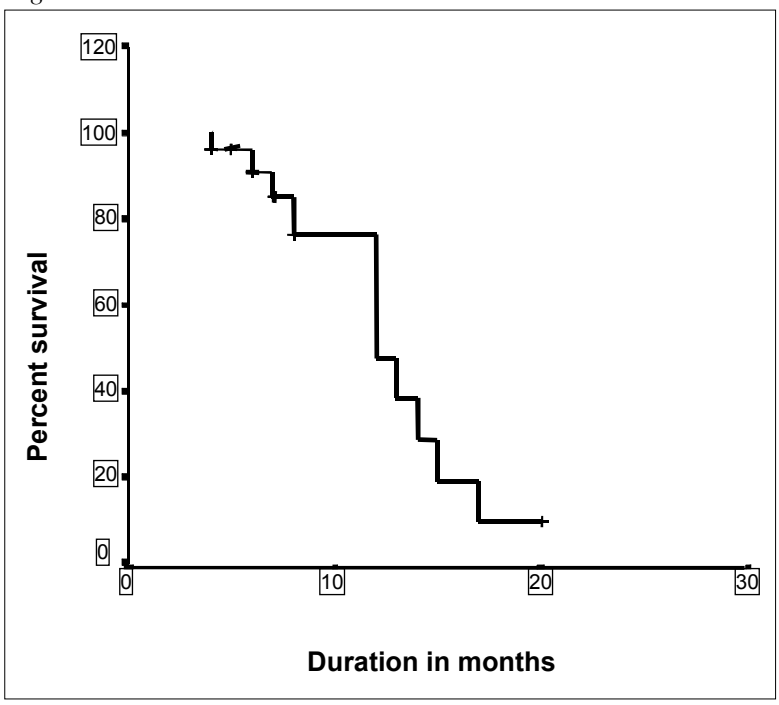


Fig.4: Actuarial survival curve



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